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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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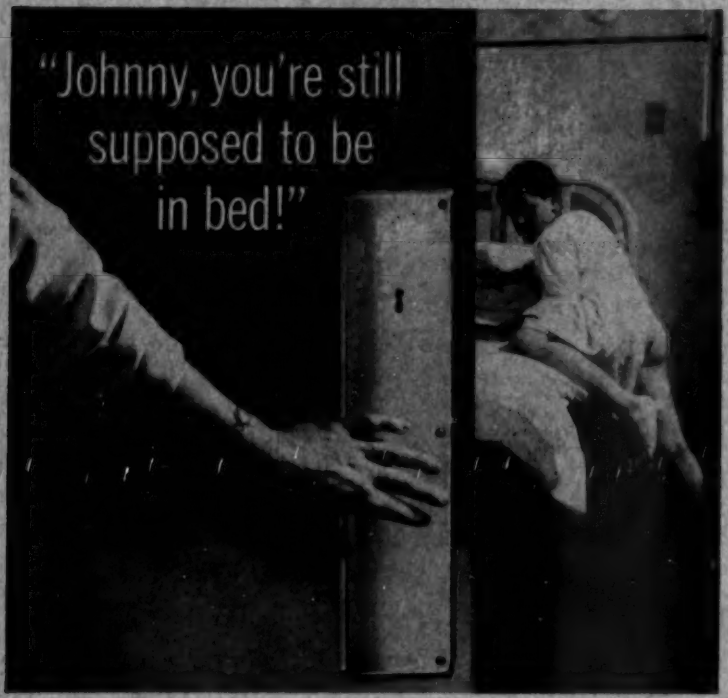

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In this latest study, each sample was analyzed separately. The analyses showed that MINUTE MAID Fresh-Frozen Orange Juice was equal to, or superior to, the home-squeezed juice in *all* of the components listed below:

TABLE

Mean Values in Samples Tested

COMPONENT	UNITS	MINUTE MAID FRESH-FROZEN ORANGE JUICE	HOME-SQUEEZED ORANGE JUICE
Betaine	mg./100 ml.	49	46
Biotin	mcg./100 ml.	0.26	0.26
Choline	mg./100 ml.	13	12
Cobalt	mcg./100 ml.	74	67
Folic acid	mcg./100 ml.	2.2	2.2
Iodine	mcg./100 ml.	0.24	0.21
Manganese	mcg./100 ml.	33	18
Nitrogen			
Total	mg./100 ml.	104	79
Amino	mg./100 ml.	22	22
Volatile	mg./100 ml.	8	7
Non-volatile	mg./100 ml.	96	72
Pantothenic acid	mcg./100 ml.	146	145
Para-amino-benzoic acid	mcg./100 ml.	4	4
Phosphorus	mg./100 ml.	19	18
Potassium	mg./100 ml.	380	290
Riboflavin	mcg./100 ml.	18	17
Tocopherols	mg./100 ml.	107	104
Vitamin A	mcg./100 ml.	19	16
Thiamine	mcg./100 ml.	87	83
Vitamin B_{12}	mcg./100 ml.	0.0022	0.0012

Although the results are again susceptible to variation according to crop and year, Fresh-Frozen MINUTE MAID was equal to the home-squeezed juice in the samples tested for the largest number of components listed; and in the mean values for iodine, manganese, potassium, Vitamins A and B_{12}, MINUTE MAID showed appreciably *higher* values.

SUMMARY

These new findings help enlarge professional knowledge of the nutrient constituents of orange juice in general and add fresh evidence that, on a cost basis, MINUTE MAID Fresh-Frozen Orange Juice has significant dietary advantages. Penny for penny, MINUTE MAID offers not only *more* Vitamin C, but also *more* of all the other vitamins and minerals listed than home-squeezed orange juice.

Taken in conjunction with the previously published findings, this should confirm the choice of physicians who recommend MINUTE MAID in place of home-squeezed orange juice.

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(4) Assn. Official Agricultural Chemists: Methods of Analysis, 7th ed. Washington: Assn. Off. Agric. Chemists, 1950.

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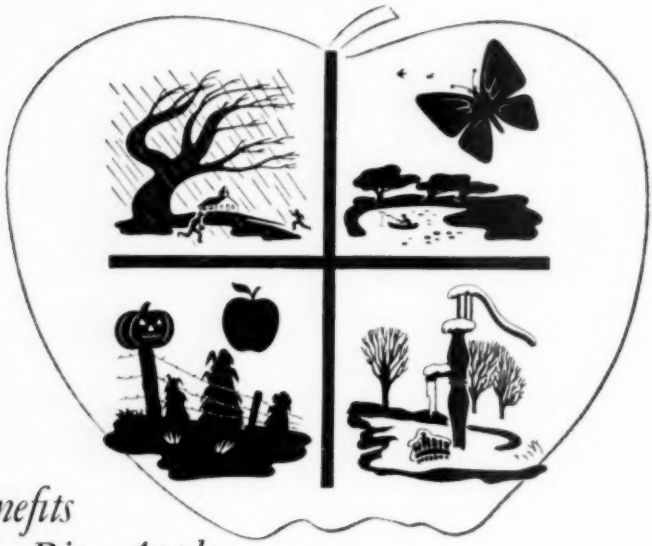

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1. Heimer, C. B., Grayzel, H. G. and Kramer, B.: Archives of Pediat. 68:382, 1951.
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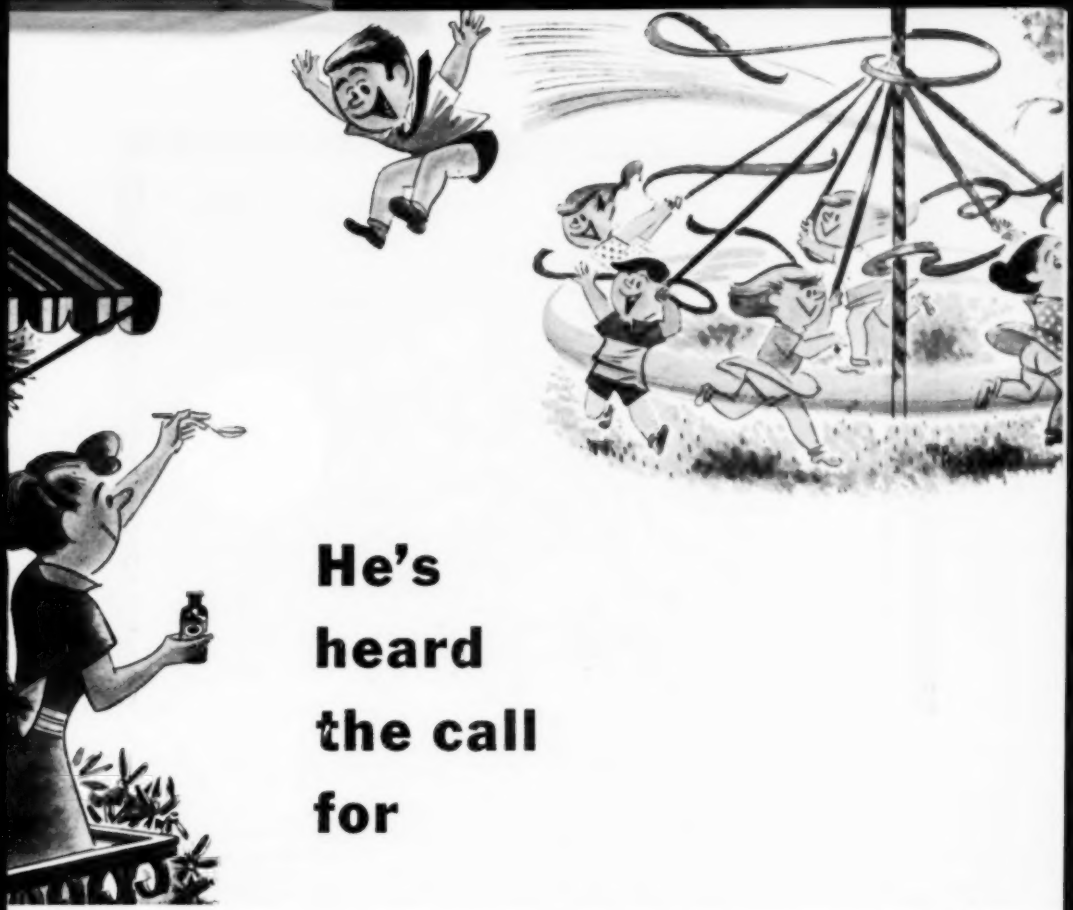

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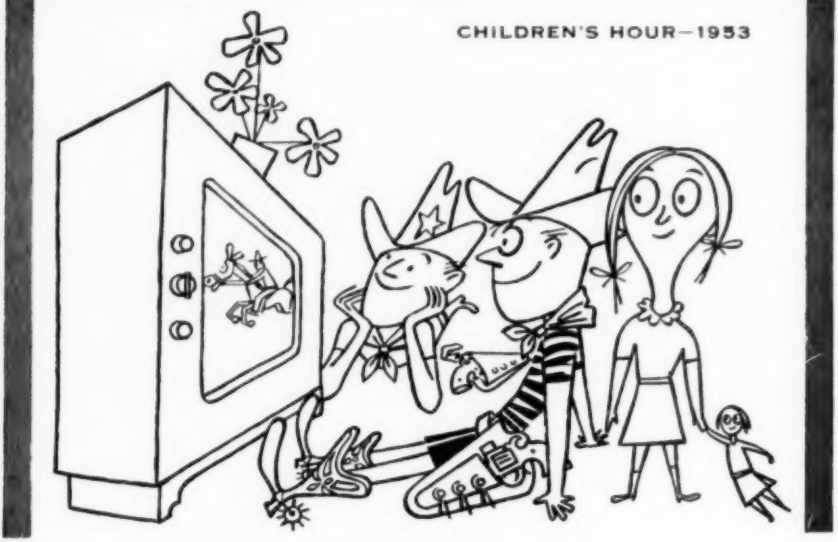

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THE JUVENILE DIABETIC*

A SURVEY OF RECENT LITERATURE

GENEVIEVE J. NEY, M.D.
New York.

When the diagnosis of diabetes has been made in the case of a child, the physician acquires two patients—the mother and the child. There are very few other illnesses which give more challenge to the doctor and, when successfully managed, provide such gratifying results. The plan for the best control possible necessitates a good working knowledge of the disease and its complications, as well as infinite patience and understanding of the many problems confronting all concerned.

Diabetes mellitus has a profound effect upon the organism as a whole, involving not only the pancreas, with resulting hypoinsulinism, but the entire endocrine equilibrium, and affecting numerous organs and systems. In diabetes the storage of glycogen in the liver and in the muscles is improverished and the tissues are unable to utilize the sugar in normal amounts. Sugars are adequately absorbed from the intestinal tract, but the liver is deficient in its function of storage of glucose as glycogen. As a consequence of these factors, a state of hyperglycemia follows, and when the renal threshold for glucose is exceeded, glycosuria appears. Glycosuria is present even in fasting states, the sugar being derived from the already impoverished liver glycogen, and finally from the conversion of body protein with subsequent weight loss. At this stage

*Submitted as partial fulfillment of the requirements of the course in Senior Pediatrics at the New York Medical College, Flower and Fifth Avenue Hospitals, New York.

there is an increased excretion of urinary nitrogen. Ultimately, the body increases fat metabolism in an effort to supply needed calories for energy and other functions. The peripheral tissues can only metabolize a certain quantity of ketone bodies transported to them after production in the liver. Again, the renal threshold is exceeded and ketone bodies appear in the urine and finally accumulate in the blood and a state of acidosis supervenes.

The etiological factors concerned are but vaguely understood to date. However, the evidence of a hereditary predisposition is widely accepted and becomes increasingly significant as the child advances in years. It is not evident at birth and rarely in early childhood but appears to be stimulated at pubescence. Many attribute the onset at this period of growth to a hyperactivity of the pituitary gland. Very frequently the child is taller, and the metabolism and bone, as well as dental developement, are more advanced than indicated by his chronological age.

The onset and nature of the disease differs markedly from that seen in the adult. In the child the disease is acute and virulent. Very often the child is first seen in a diabetic coma. The diagnosis is usually made without too much difficulty if the physician keeps such a probability in mind. The finding of glycosuria, elevated fasting blood sugar, together with certain symptoms elicited, make the diagnosis relatively simple. Loss of weight, polyuria, polydipsia, enuresis, coma or acidosis, anorexia and fatigue are the most common initial findings in order of frequency. A glucose tolerance test is of value in the child to eliminate the nondiabetic.

Some physicians believe that the treatment of a diabetic child is essentially the same as that of an adult. However, this can scarcely be accepted as an adequate description of the whole picture and may lead to poor control and many unnecessary problems. Adequate management must be designed to meet the needs for growth and development, to integrate the various endocrine glands and to assist the young patient in the attainment of adulthood well prepared to adjust to the problems of a useful life. Hence, any such long-term program requires periodic readjustment with foresight in order to satisfy the progressive needs of the patient. Then again, behavior problems commonly occur in the young diabetic patient and it is important that they receive due attention so that the patient will be equipped, socially and emotionally, to meet the

difficulties imposed by his diabetic state. In these respects it can be readily understood why the juvenile diabetic presents a rather unique perplexity to the attending physician.

For purposes of simplification, the treatment of the diabetic child can be divided into the following categories: (1) Treatment of diabetic acidosis or coma and the immediate postacidotic period, (2) Establishing an adequate diet and insulin requirement, (3) Maintenance and supervision.

Any diabetic in a state of acidosis or coma is a medical emergency. Blood should be immediately drawn for determination of the blood sugar and carbon dioxide combining power. Urine is collected, if necessary by catheterization, for sugar and acetone examinations. An indwelling catheter may be necessary to obtain further specimens as needed.

The salient features of therapy in the first hours are the correction of dehydration and the replacing of the insulin deficit. Dehydration results in hemoconcentration and this, in turn, is responsible for loss of renal function increasing the severity of the acidosis. Along with the loss of body water there is a loss of electrolytes.

Insulin given early and in adequate dosage is of prime importance. It may be stated in general that a child between the ages of one and five years will require in the neighborhood of 25 to 100 units of insulin while older children need 75 to 300 or more units to restore acid-base equilibrium.

At the Children's Hospital, Washington, D. C., it is felt that it is not wise to use glucose in the early hours of coma treatment until a significant drop in blood sugar indicates the utilization of this sugar. Carbohydrate is then given intravenously as a 5 per cent glucose solution, and, when feasible, by mouth.

Fluids are replaced by the use of physiological saline, Ringer's lactate, or one-sixth molar lactate solution. The amount of fluid required will vary with the degree of dehydration and, of course, the age of the child. Gastric lavage is performed routinely in many hospitals and, if necesary, sodium bicarbonate solution can be left in the stomach before withdrawing the tube. Such a procedure will relieve dilatation and accumulation of gastric secretions, blood by diapedesis, etc., and, in addition, will serve to eliminate vomiting in the post-acidotic stage, thus making it possible to institute oral

feeding more quickly. The intravenous administration of fluids is discontinued as soon as it is demonstrated that the child can take a sufficient amount of nutrient fluids by mouth and retain them.

If shock is present, there may be evidence of peripheral collapse. Adrenal cortical extract should be given and blood or plasma following 400 to 500 cc. of physiological saline solution.

Since an infection of some sort is frequently the precipitating factor in diabetic coma, antibiotics must be given before adequate control will be secured.

Replacement of intracellular potassium has received much attention in recent years. If it is necessary to maintain the patient on parenteral therapy for any length of time, potassium must be supplied. Adequate renal function is essential before potassium is added to the intravenous therapy.

When the child is fully conscious and evinces a desire for fluids, oral nourishment may be begun in small quantities and at frequent intervals. Carbohydrate should be given in relatively high amounts and in a readily digestible form. Fruit juices, ginger ale, skimmed milk, gelatin desserts provide fluid as well as caloric requirements. It is advisable to give feedings at three-hour intervals in this postacidotic phase and administer insulin as indicated by the amount of glycosuria, blood sugar levels, and the age of the child.

Successful stabilization of the juvenile diabetic patient is dependent in a large measure upon the thoroughness of the initial program of control. In any case it is advisable to hospitalize the patient as soon as the diagnosis is made in order that the condition may be brought thoroughly under control. The state of mind as well as the physical condition of the patient will be modified by the thoroughness of the initial program of care. The longer the disease is incompletely controlled, the more difficult it will be to attain and maintain complete control. Complete control implies the absence of sugar in the urine, absence of insulin reactions and maintenance of an approximately normal blood sugar level.

With a well planned regime, both the parent and the child will come to accept the disease and its limitations with greater ease and understanding. The complete stabilization of the diabetic child requires several weeks or more. It is best to keep the child in the hospital during this period of time since better control cannot only

be obtained, but the time can be used for the teaching of the child the techniques of diabetic management, such as the administration of insulin, the examination of urine, the dietary management, and the keeping of good records. The child should be expected to assume an increasing responsibility for his daily care. Much of this will depend, quite obviously, upon the age of the child.

At the same time, it is the responsibility of the doctor to educate the family in the acceptance and understanding of the problems which will soon confront them in making the home life of the child as near normal as possible. The family should be encouraged to adopt as similar a diet to that of the patient as is feasible. In this way the child is not singled out for special attention which may very well bring about family friction. The importance of family cooperation cannot be overemphasized to minimize potential psychological problems. Diabetic camps have been of great help to patient, parent and physician in enabling the child to lead a normal life.

The prescribed diet should satisfy fully the needs for optimum nutrition, and be readjusted periodically to meet the changing demands of maturation. The total calories required are first determined. A child needs approximately 1.5 gm. of protein per pound of body weight and about twice this amount of carbohydrate. The remaining calories are made up in fat.

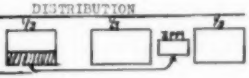
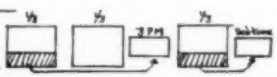
Every diabetic child requires insulin. It is fairly generally accepted that the diabetic patient is not thrown into acidosis by dietary indiscretion in the sense of overeating within the limits of appetite, but by insufficient insulin. The onset of acidosis and coma in the juvenile diabetic can be ascribed invariably to factors of infections and/or failure to increase the dose or total omission of the insulin.

During the period of greatest sexual development a radical change in the character of the disease takes place, the disease becoming more severe. The insulin requirements mount rapidly and the nutritional needs increase at a rate sufficient to support the rapid growth and essential physical activity. It is believed that the increased activity of the various endocrine glands at this period of development tends to partially neutralize the effect of exogenous and endogenous insulin. Then too, the adolescent is making an emotional adjustment at this time and emotional stress

as well as physical exercise are major factors controlling the response to therapy.

Insulin reactions are common, and their recognition may be more difficult than in the adult. Both the child and the mother should be thoroughly familiar with these reactions and the knowledge of how best to prevent them. Listlessness, negativism, peevishness, and circumoral pallor are signs and symtoms commonly found in the child. Headache, nausea and vomiting also may occur. The time relation of these reactions will depend upon the type of insulin used.

In general, one of the rapidly acting insulins, regular or crystalline, is best used for children under five years of age, and protamine insulin, globin insulin or nonprotein nitrogen insulin with or without one of the rapidly acting insulins is used for children above this age. The success of the various insulins in providing adequate control varies greatly from patient to patient and from doctor to doctor. In practically no case does a single dose of protamine zinc insulin control the diabetes satisfactorily. A single dose of globin insulin is satisfactory in a small number of cases. Many find that a mixture of protamine zinc insulin and regular insulin, 2:1 or 3:1, fifteen minutes before breakfast and a small dose of regular insulin before supper is a most effective plan of therapy.

INSULIN	TIMING	DISTRIBUTION
Globin	1 dose one hour before breakfast	
NPH	1 dose one hour before breakfast	
NPH and RI (mixed)	1 injection 1/4 hour before breakfast	
NPH and RI (mixed) a.c.b.) and NPH before supper	2 injections 1/4 hour before breakfast and 1/4 hour before supper	

Duncan states that if diabetes is so mild that slow action of a single dose of protamine zinc insulin (PZI) is adequate to control the diabetes during the daytime—when three meals are given in fairly close succession—it should be clear that a small dose of either

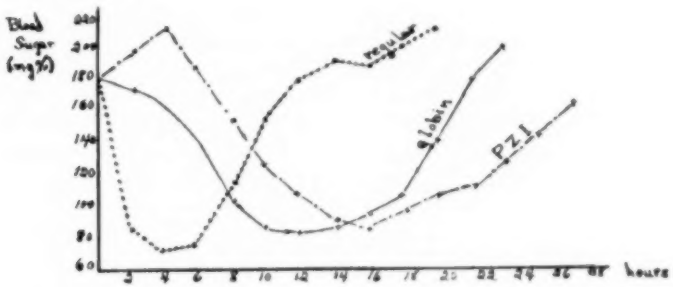
globin insulin or nonprotein nitrogen (NPH) insulin that has maximum effect during the daytime should replace the PZI to avoid the risk of a hypoglycemic reaction early in the morning from the long-acting PZI.

Hypoglycemic reactions are not necessary in achieving good control of the diabetes, but knowledge of when they are most likely to occur is important, especially in regulating the distribution of the diet and the dosage of insulin. Duncan has suggested three plans for the administration of insulin. They may be summarized as follows:

Plan 1—Globin insulin. When the 3P.M. blood sugar reaches normal, no further increase should be made. NPH insulin lends itself well to a mixture with regular insulin (RI) without appreciably affecting the characteristic effectiveness of the latter.

Plan 2—NPH and RI (mixed). Regular insulin is increased daily until no or very little glycosuria occurs in the forenoon. The NPH insulin is increased until the afternoon and evening fractions are free of glycosuria.

Plan 3—RI is increased until there is no glycosuria in the forenoon. NPH is increased until glycosuria in the afternoon is corrected. Evening NPH is increased cautiously by small quotas of two to four units at two-day intervals until the overnight glycosuria is controlled.



When the glycosuria is reasonably well controlled, four blood sugar determinations, one before each meal and at bedtime, are done. Glycosuria serves as a guide in increasing the insulin, and while it persists, frequent blood sugar determinations are unnecessary. When the glycosuria is corrected, the diabetes is nearly

controlled in most cases and a fine adjustment of the insulin dosage can be made, based on four blood sugar determinations in one day.

The preceding graph, from Duncan, demonstrates the comparative effects of 60 units of regular, globin, and protamine zinc insulins when administered subcutaneously to a hyperglycemic patient who received 20 grams of carbohydrate by mouth at two-hour intervals during the observation.

It is the firm conviction of many today that continuous aggressive treatment of diabetes, directed toward the maintenance of physiologic conditions, including normal levels of blood sugar, is of the greatest importance in reducing the incidence and severity of degenerative complications. In a recent survey made by Wilson, Root and Marble studying the degenerative vascular lesions in young patients on a rigid scheme of control compared to those following a "free diet" regimen as advocated by Tolstoi and others, 44 per cent of patients in the controlled group showed advanced blood vessel calcification despite 20 or more years of diabetes, whereas 80 per cent demonstrated advanced arterial calcification in the group following the free diet regimen for a similar period of years. The evidence of retinopathy was even more marked in the poorly controlled groups and those on a free diet. Hence, by good control, one can at least minimize or postpone vascular complications.

In regard to the complications seen in childhood diabetes, of particular concern are the development of acidosis and coma, infections, hepatomegalia, degenerative changes, and the occurrence of retarded growth and development. Lipodystrophy, or the absorption of fat at the site of insulin injections, is often seen among children. The condition can be avoided by using areas not usually seen and by frequently changing the site of the injection.

Diabetic acidosis and coma have already been briefly discussed. Infections most frequently seen in diabetic children are tuberculosis and infections of the urinary tract and skin. The prognosis for the diabetic with pulmonary tuberculosis is still poor, and tuberculosis ranks about second to coma as the cause of death in children with diabetes. Infections of other types have been overcome for the most part with the present-day antibiotics and chemotherapeutic agents.

Hepatomegaly occurs in those children with severe diabetes

which has not been brought under satisfactory control. It is generally believed that this is due to the deposition of fat in the liver. However, with proper insulin control these large livers may be reduced to normal size within several weeks.

The incidence of degenerative complications in juvenile diabetes is still far greater than many believe. One of the earliest evidences of this is the occurrence of cataracts. They may not be progressive, and in any case can be successfully treated surgically. Retinitis is another rather common sequelae and is often reversible. However, in the more severe form, retinitis proliferans, damage is permanent. Arterioselerosis appears inevitable as a complication in this disease. Some believe it to be a result of improper metabolism of fat and the ingestion of lipotropic substances as choline, and lipocaic may postpone its occurrence.

Growth has been unimpaired among those who maintained proper control.

From the standpoint of prophylaxis, early detection of the disease is of prime importance. In this way prompt care may be instituted and with the least difficulty. It would indeed be advisable to periodically check all children with a familial history of diabetes by means of a glucose tolerance test say every two months for the first year and every six months thereafter. In the case of known diabetics, during periods of infection, daily urinalyses, with glucose tolerance tests at the onset and the end of the illness, are not indicated, but are a wise procedure in those with a familial tendency. After such infections, these children should be repeatedly checked by urinalyses for a period of months.

Today, the outlook for the juvenile diabetic is good. Life has been considerably prolonged and much progress in prevention and control of complications has been made. Parenthood has been possible although not without some difficulty in long-standing diabetics. However, they should be encouraged to seek a nondiabetic partner in view of the part of heredity in causing diabetes in the offspring. Special care during pregnancy is advised to better insure its successful culmination.

In selecting an occupation, a diabetic should attempt to enter one where regularity of meals, physical activities and rest can be assured.

Up to date few studies have been made of long-standing diabetes,

that is, following the juvenile diabetic through adulthood. Hence, it presents a real challenge to any doctor in that in following his patients along, he may evaluate the success or failure of his plan of therapy. In a sense, both doctor and patient are pioneers in a fairly virgin field of medical knowledge and each can contribute much of great value to others, since they may point the way to the better treatment of those who follow them.

CONGENITAL CATARACT AND MATERNAL SMALLPOX. (Journal of Tropical Medicine and Hygiene, London, 55:99, May 1952). It is well-established that some virus diseases in the pregnant woman may be followed by various congenital anomalies in the child. This has been shown particularly clearly in maternal rubella, but is also possibly true of varicella, mumps, influenza, hepatitis, and poliomyelitis. In this paper a child is described who had a cataract involving the whole of the left lens. During the third month of pregnancy the mother had had a severe febrile disease, which presumably was smallpox. It is assumed that the infant's congenital cataract may have resulted from viral damage to the developing embryo, in the same way as has been described in cases of maternal rubella.—*Journal A.M.A.*

TERRAMYCIN IN TREATMENT OF WHOOPING COUGH. (Monatsschrift für Kinderheilkunde, Berlin, 100:359, Aug. 1952). Fifty children, including 31 infants, with whooping cough were treated with terramycin. The drug was given orally in daily doses of 50 mg. per kilogram of weight (divided into four doses), and this dosage was continued for from one to two weeks. The results were excellent in about one-third of the patients and moderately good in another third. In the remaining third the treatment failed. These results were about the same as those obtained with aureomycin in another group of whooping cough patients. Like this latter drug, terramycin can be recommended for children who are seriously ill with pertussis because it may help to reduce the mortality, particularly in young infants.—*Journal A.M.A.*

IS THE CAUSE OF POLIOMYELITIS ALWAYS THE SAME?

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It is generally believed at the present time that poliomyelitis is a communicable disease caused by a virus. However, this broad definition excludes other conditions to which the term "poliomyelitis" can also be applied. The meaning of the Greek words from which "poliomyelitis" is derived implies inflammation of the gray matter of the central nervous system regardless of the etiology. The modern definition, on the other hand, intimates that all cases of this disease are caused by a virus. This conclusion has originated from the fact that a "virus" has been isolated from a small number of cases during epidemics of this disease and it is concluded unjustifiably, therefore, that every case of poliomyelitis has the same cause. The restricted modern usage of the term "poliomyelitis" undoubtedly accounts for much of the confusion that exists today regarding this disease. From the laboratories and as a result of animal experiments unjustified inferences have emanated that are presumed to be applicable to all cases of poliomyelitis encountered in medical practice. Van Rooyen and Rhodes[1] (1948) make the following significant remark regarding this fact: "Theories of the pathogenesis of human poliomyelitis have resulted very largely from experimental work carried out on monkeys rather than on observations on the patient." It should be stressed at this point that physicians in practice have seen and will continue to see the majority of the cases of poliomyelitis.

The diagnosis of poliomyelitis is often very difficult and hazardous. Reports of the disease are often uncertain and frequently erroneous. Diagnosis is not based upon specific, critical tests, but usually upon the physician's judgement. During epidemics of poliomyelitis as many as fifty different diseases have been called "poliomyelitis" and patients have been sent to contagious disease hospitals where the diseases were sorted out.[2] In an epidemic of poliomyelitis in Tennessee, in 1941, there were erroneous and highly questionable diagnoses in a considerable proportion (over 30 per cent) of the cases, according to Lumsden.[3] Anderson[4] (1949) says; "Much of our uncertainty regarding poliomyelitis

has stemmed from an inability to define the disease with any degree of exactitude." "One never makes a diagnosis of any condition which one does not have in mind, and if one's mind is occupied with one disease, mistakes are certain to be made."[4] Many illnesses, some unrecognizable, occur during the season when poliomyelitis is prevalent. It is unjustifiable and unscientific to consider any of these to be a form of poliomyelitis until proved conclusively to be such by specific, scientific tests. Silverman[5] (1952) states regarding these unrecognizable cases that they can have only an academic interest as relating to the epidemiology of poliomyelitis.

Virus recovery tests are expensive, require time, are clinically impractical, and are carried out, therefore, in an insignificant number of cases of poliomyelitis during epidemics of that disease. Further, there is no correlation between the presence of antibodies in an individual and the occurrence of poliomyelitis. An appreciable number of patients fail to develop antibodies consequent to an attack or to show any increase later in the convalescent stage. Esquimos and Liberian negroes, where poliomyelitis is unknown to have occurred, have 90 to 100 per cent neutralization tests for their sera, according to Landon and Smith[6] (1934). Harmon and Harkins[7] (1937) presented evidence that poliomyelitis may develop in the presence of neutralizing antibodies. In a series of 183 patients convalescent from poliomyelitis, Landon[8] (1938) found that nearly 40 per cent showed no antibody. Burnet[9] (1939) concluded that poliomyelitis antibody is not the result of exposure to, or infection with, the virus of poliomyelitis.

Inconclusive evidence of a virus etiology in all cases of poliomyelitis is demonstrated by other facts. For example, in many cases where the diagnosis is made with certainty, virus recovery tests have proved to be negative. Even in fatal cases, it has not been possible in some cases to demonstrate a virus in the feces or in the spinal cord.

In the vast majority of cases of poliomyelitis, the criteria for diagnosis has depended almost entirely on the presence of an epidemic of the disease, neurological signs and the presence of a pleocytosis. However, ten per cent or more of the cases of poliomyelitis that are reported have normal spinal fluid cell counts and pleocytosis can occur, together with neurological signs, in

conditions other than infectious diseases. In the so-called abortive cases of poliomyelitis, there are no characteristic signs and the spinal fluid is usually normal; the diagnosis is made merely by implication.

During the past century many etiological factors have been suggested to explain poliomyelitis which may be classified in three principle groups: 1 Infectious, 2 Toxic, and 3 Metabolic.* Poliomyelitis investigations during the past forty years, however, have been confined almost exclusively to the infectious (virus) origin of the disease. The insistence that there is only one cause of poliomyelitis has obstructed investigation of all possibilities.[10, 11] In referring to the virus origin of this disease, Lumsden[12] (1938) states: "To some of us it does not appear to square with the facts obtained by epidemiological studies of the disease. It seems too elastic, too restful."

In view of the fact that the vast majority of the cases of poliomyelitis occuring during an epidemic of this disease are not subjected to viral recovery studies or any other accurate specific scientific test, but rather conclusions are based on the supposition of a virus infection, it is pertinent that we critically examine other causal factors that may produce the disease. "Poliomyelitis" is in fact, as will be shown, a collective name for a symptom complex which is produced under different circumstances by different causes.. Unfortunately, the general impression has been that it can be caused only by a virus. In the present state of uncertain and incomplete knowledge a study of the plural etiology of poliomyelitis should be fruitful.

Lovett[13] (1908), in reporting the 1907 epidemic of infantile paralysis in Massachusetts, said that it may be simply the clinical expression of the reaction of the spinal cord to one of several causes, of which infection may be one. Flexner[14] (1910) also suggested a possible plurality of causes of poliomyelitis. Still[15] (1915) raised the important question of plurality of causes when he asked: "May the lesion result from many different causes, infective and otherwise?" He pointed out that the clinical course and apparent exciting causes of some of the sporadic cases at least suggest the possibility that similar pathological changes may be due to dissimilar causes.

*The metabolic cause of poliomyelitis has been described by Huffman[17] (1911); Helms[18] (1941); and McCormick[19, 20] (1942, 1943, 1944, 1950).

Only by exercising a broad view shall we be able to extend and amplify our present ideas and eventually correlate the symptom-complex with the actual causes. Taylor[16] (1902) stated significantly concerning poliomyelitis: "Its final place must be determined by a study of its cause or causes, as related to various other degenerations and inflammations of the nervous system."

TOXIC CAUSES OF POLIOMYELITIS

Many reports have appeared in the medical literature of poliomyelitis following poisoning by organic and inorganic poisons; these have been reviewed by the writer.[10, 24-32] In the present report the occurrence of poliomyelitis as a result of bacterial toxins and as a complication or sequel of infectious diseases will be considered primarily.

Many of the older writers noted the supervention of poliomyelitis during the acute stage of the infectious or febrile diseases or during convalescence therefrom. Medin,[33] Strümpel,[34] as well as Zuppert,[35] found that many cases of poliomyelitis occurred in connection with the infectious diseases, including measles, scarlet fever and typhoid fever. Bartholow[36] (1887) states that cases frequently occur during the course or convalescence from the exanthemata and other acute febrile affections and a causal relation is considered to exist. Bassette[37] (1892) reported a series of eighteen cases of post-infectious paralytic affections and reviewed the literature on the subject. Some of her cases showed the occurrence of either neuritis alone, or poliomylitis alone, or both of these diseases conjointly, during or following measles, scarlet fever, diphtheria, whooping cough, mumps, etc. Caverly[38] (1894), in describing an epidemic of poliomyelitis in Vermont in 1894, stated that physicians practicing in the epidemic area at the time of the epidemic noted that the usual diseases of children were accompanied with exaggerated nervous symptoms. Headache, convulsions and delirium were common. Roberts[39] (1894), writing on poliomyelitis, states that it sometimes follows one of the acute exanthemata or other febrile diseases. Bruns and Windsheid[40] (1897), noting the induced disease of the spinal cord caused in experimental animals by a number of organisms, say that it is probable that a great number of disease germs have the power to produce poliomyelitis anterior. Holt[41] (1897) found that

12 per cent of a total of 566 cases of poliomyelitis came on as a sequel of some acute disease, notably diarrhea, scarlet fever, typhoid fever, whooping cough and vaccination. Hoch[42] (1905) says: "There is sufficient evidence at hand to consider the disease as a rule of an infectious nature, however, not depending upon a specific micro-organism but resulting from bacterial infections of various kinds, and at times from other poisons." Cotton[43] (1906) states: "It is known to follow or to complicate acute infectious diseases, such as measles, scarlatina and typhoid fever." Oppenheim[44] (1908) stated: "It is admitted that an attack may follow in the wake of infectious diseases, such as measles, scarlet fever and whooping cough; the disease has occasionally developed in connection with vaccination." Claud[45] (1911), stated as a result of his observations, that classical poliomyelitis is probably the result of diverse infectious agents. Chapin and Pisek[46] (1919) point out that poliomyelitis may be seen in connection with certain infectious fevers, such as scarlatina and typhoid fever. Pritchard[47] (1924) states that poliomyelitis is often a sequel of the febrile infections of childhood, especially scarlet fever, measles and diphtheria. Lumsden[1] (1941) noted an increased incidence of smallpox in the same counties scattered throughout Tennessee which coincided with an epidemic of poliomyelitis in the same districts. He also pointed out that there was a markedly higher morbidity and mortality from diphtheria in children under five years of age in the same localities. Vaquez Lapuente[48] (1943) reported that paralysis of the same extent and degree is caused by poliomyelitis or any infection. In 97 of 100 children, paralysis followed typical poliomyelitis in 17 cases; measles in 28 cases; and various other general infections in 52 cases. Piszcek[49] (1952) pointed out that in 1943, in Cook County, there were 1,262 poliomyelitis cases with 108 deaths. At the same time an epidemic of diphtheria was prevailing in Chicago.

It is not surprising that such reports as the above should have appeared in the medical literature because the fundamental action of a disease producing organism is dependent on the toxin that it elaborates rather than on the organism itself. Putnam[50] (1895) states regarding this fact: "It has been made pretty certain that the signs we think of as characteristic in the nervous affections following infectious processes are due far more to the toxic sub-

stances which are developed in the course of bacterial action than to the micro-organisms." He states further: "The prostrating influence of the original struggle, though it may end in the apparent defeat of the infective agent, is liable to search the hidden weaknesses of the nervous system and to lay it at the mercy of morbid agencies with which it would otherwise have been able to cope successfully."

Experiments with animals indicate that by using diverse organisms non-specific toxins can cause poliomyelitis. Oppenheim[44] (1908) states regarding these experiments: "Of recent years, by experimental introduction into animals of micro-organisms such as B. typhosus, B. influenza, B. diphtheriae or its toxin and also B. coli, anatomical changes in the spinal cord have been successfully produced, which, in their localization and nature, call to mind those of acute poliomyelitis." Lovett[13] (1908) makes a similar statement. He says: "The injection experiments prove that certain metallic poisons, bacteria and toxins have a selective action on the motor cells of the anterior cornua when present in the general circulation; that the paralysis of this type may be largely unilateral; that the posterior limbs are always more affected than the anterior; and that the lesions in the cord in such cases do not differ from those in anterior poliomyelitis."

The streptococcus has been the most intensively studied and the most frequently mentioned bacterium capable of producing poliomyelitis. Roger[51] (1891) injected rabbits intravenously with streptococci and noted, on examination of the nervous system, swelling and vascular degeneration of the anterior horn cells with atrophy of their nuclei. Bourges[52] (1893) inoculated animals subcutaneously and intravenously with erysipelas organisms, and these animals developed paraplegia, sphincter paralysis and muscular atrophy. Microscopical examination of the nervous system revealed vessel changes, cellular exudations, especially into the gray matter, and degeneration of the ganglion cells. Vidal and Bezancon[53] (1895) investigated the production of myelitis by means of streptococci injections. The animal used for the experiments was the rabbit. A total of 116 animals were injected with streptococci taken from 89 different sources and endowed with varying degrees of virulence. Of the 116 inoculations, seven animals, or six per cent, later developed paralytic symptoms. At autopsy,

degenerative lesions were found microscopically in both the gray and white matter. The gray matter throughout the cords was more or less affected, but especially in the lumbar enlargement. The ganglion cells of the anterior horns showed marked degenerative changes up to complete destruction. Bacteriological examinations of the rabbits' cords did not demonstrate the presence of streptococci, whereas, they were found at times in the viscera and blood. The legitimate conclusion was reached that the observed lesion was produced by soluble toxins and not by actual bacterial action.

A considerable amount of research work in the production of poliomyelitis with the streptococcus has been done in recent years, chiefly by Rosenow.[54] Although Rosenow and others have been able to demonstrate lesions characteristic of poliomyelitis in their studies, the objection to this work is the fact that they have considered the streptococcus to be the only cause of poliomyelitis.

The cases of poliomyelitis which have followed the injection of penicillin during epidemics of poliomyelitis in recent years could obviously be the result of the toxins of the streptococcus and other organisms rather than of the injection itself. Penicillin is bacteriostatic, not antitoxic. It is a well-known fact that the administration of penicillin in upper respiratory tract infections will be followed in some cases by sequelae despite the clearance of the original infection. This fact is illustrated by the development of acute glomerular nephritis* following scarlet fever and the rheumatic manifestations following streptococcus infections.

According to Gowers[55] (1888) limited atrophic paralysis sometimes occurs in typhoid fever, especially during convalescence, and he believes that in some cases the lesion is acute anterior poliomyelitis. Gumpertz[56] (1900), Lepine[57] (1903) and others have reported the appearance of poliomyelitis during the course of typhoid fever. Osler and McCrae[58] (1923) point out in their textbook, under complications of typhoid fever, that poliomyelitis may occure with the symptoms of acute ascending paralysis and prove fatal in a few days. "More frequently," they state, "it is less acute, and causes either a paraplegia or a limited atrophic paralysis of one arm or leg."

Vincent[59] (1883) used typhoid bacilli for his injection material in experiments on animals. He found in addition to degeneration

*Silverman[8] (1952) reported a case, a boy 16 years of age, with glomerular nephritis followed in four days by poliomyelitis.

of the anterior horn cells some proliferation of the neuroglia. Alajonine et al.[60] (1928) reported a case of poliomyelitis in a patient following antityphoid vaccination.

Gilbert and Lion[61] (1892) produced poliomyelitis in experimental animals with the streptococcus and Thoinet and Masselin[62] (1894) with the colon bacillus. Marinesco[63] (1900) produced lesions analogous to those of human poliomyelitis with the influenza bacillus, as well as with the streptococcus. Klingman[64] (1911) reported a case of anterior poliomyelitis caused by an acute gonorrheal infection and Oppenheim[44] saw one case of poliomyelitis preceded by a severe gonorrhea. Syphilitic acute anterior poliomyelitis has been described by a number of writers.[65-70]

In diphtheritic paralysis, as a result of toxins, the nervous system is involved both centrally and peripherally, that is, both the anterior horn cells and the peripheral nerve trunks are affected. Diphtheritic paralysis is usually not seen until the acute stage is passed and more often during convalescence. Bassette[37] reported a case of multiple neuritis and poliomyelitis after diphtheria in a four-year-old child. According to the experience of Mirabell[71] (1934), diphtheria may reproduce so thoroughly poliomyelitis in its paralysis, meningeal features, motor and sensory disturbances that a differential diagnosis is not always possible. Welch and Schamberg[72] (1905) point out that there are instances reported in which paralysis has occurred in persons who, presumably, were affected with the diphtheria poisons without having exhibited any of the ordinary symptoms of the disease.

Endriquez and Hallion[73] (1894) found that the toxins of diphtheria when injected beneath the skin of dogs, if the dose is not too large, may cause intense congestion of the gray matter of the cord, with hemorrhages and foci of inflammation, characterized by formative irritation of the neuroglia and destruction of the nerve elements. They also produced symptoms suggesting a similar process in the ape.

It is a well-known fact that in diphtheria antitoxin laboratories, guinea pigs used in routine tests of the strength of diphtheria toxins and antitoxins not infrequently develop paralysis. The animals which survive the inoculation for three weeks or longer suffer from paralysis during the third or fourth week. The paralysis may be slight, affecting but one limb, or somewhat em-

harrassing the respirations, or it may be severe and cause sudden or gradual death. Ehrlich[74] (1904) concluded that these paralytic phenomena resulted from the specific action of a portion of crude toxin which he designated *toxon*. Dryer and Madsen[75] had, however, worked with a toxin which, when injected in appropriate doses, caused such a paralysis. Jungeblut [76] (1934) observed marked lesions in the anterior horn cells of the spinal cord of monkeys dying with diphtheritic paralysis.

Lewis [77] (1906) injected 209 guinea pigs with diphtheria toxin-antitoxin containing one-tenth the standard antitoxic unit which neutralizes theoretically 10 minimal fatal doses. Nine, or four and three-tenths per cent, became paralyzed. Eight hundred and fifty-eight animals were injected with a toxin-antitoxin mixture containing the full standard antitoxic unit which neutralizes theoretically one hundred minimum fatal doses of diphtheria toxin. Two hundred and fifty-nine, or thirty and one-tenth per cent, of these animals became paralyzed.

The coexistence of influenza and poliomyelitis has been noted by a number of writers. Crookshank[78] (1920) traced the history of epidemics of influenza for about 450 years and pointed out the existence of poliomyelitis and polioencephalitis coinciding with epidemics of this disease. Goldflam[79] (1891) reported a case of polioencephalitis, superior and inferior and anterior poliomyelitis after influenza, with fatal termination. Bassette[37] points out that during and following influenza many forms of nervous diseases, functional and organic, have occurred, including neuritis, myelitis, cerebritis, meningitis and combinations of these inflamations. She reports a case, a boy, six years of age, who at the height of an epidemic of influenza had all the features corresponding to a localized poliomyelitis. She states that an unusual number of cases of juvenile paralysis were brought to the Polyclinic during the declining months of the epidemic of influenza. In 1899, Burckhard[80] reported a case of acute poliomyelitis after an attack of influenza in a 15-year-old girl. Lord[81] (1907), writing on Influenza in Osler's Modern Medicine, points out that acute anterior poliomyelitis can follow an attack of influenza. Brorstrem[82] (1910) noted the simultaneous occurrence of acute infantile paralysis and influenza in the Swedish County Tingeryd in 1905, 1906 and 1907, and in the spring of 1908. He maintained that infantile paralysis

and influenza are the same. Hiller[83] (1922) noted an increased incidence of poliomyelitis cases during an influenza epidemic and Chalier[84] (1942) observed an epidemic of poliomyelitis cases following one of influenza.

According to the older writers, poliomyelitis was not infrequently preceded by diarrhea; "foul bowels" was often mentioned as a factor. Osler and McCrae[58] state: "An interesting sequel of dysentery is paralysis. Woodward reported eight cases. Weir Mitchell mentions it as not uncommon, occurring chiefly in the form of paraplegia." Francis[85] (1917), of the Cook County Contagious Disease Hospital, Chicago, was able during an epidemic of poliomyelitis to produce a paralytic condition in rabbits resembling poliomyelitis by the injection of the Shiga dysentery bacillius. Doerr and Seidenberg[86] (1936) found that the dysentery toxin acts on the cecum and the lumbar and cervical enlargements of the spinal cord in the rabbit regardless of how it is introduced. De Teyssiew[87] (1921) reported acute poliomyelitis following the injection of anticholera vaccine.

Cholera infantum, also known as intoxication, toxicosis, infectious diarrhea, and summer complaint, not infrequently resulted in paralysis. In a series of 350 cases of poliomyelitis reported by Sinkler[88] (1890), twelve followed cholera infantum. This disease was attributed to bacterial toxins in food or in the intestinal tract as a result of heat and humidity in the summer and autumn. Potter[89] (1887) attributed the cause of cholera infantum to alkaloids in the food. He pointed out that there are five poisonous alkaloids that bear a relation to summer diarrhea, i.e., neurine, muscarine, choline, mydalein and a substance of undetermined position. The action of the first three of these he states is identical; the most important symptoms produced by a fatal dose are salivation, vomiting and diarrhea, dyspnea, paralysis and death.

Corresponding with this disease of infants, the cholera morbus of older children was characterized by vomiting and diarrhea; it was not infrequently followed by paralysis. Cholera morbus was attributed to fermentative changes in the ingesta. Both cholera infantum and cholera morbus showed exacerbations with hot weather, reaching their peak in "dog day" weather and ameliorating with the advent of cooler weather which corresponds with the poliomyelitis of today.

Malarial paralysis has been reported by a number of writers. Sterian[90] (1897) described a case of acute anterior poliomyelitis of malarial origin in an adult.

Bassette[37] (1892) reported a case, a five-year-old child, with paralysis of the left leg following mumps. She considered this case one of probable neuritis and poliomyelitis. Missimilly[91] (1913) reported a case of poliomyelitis following mumps in which there was complete flaccid paralysis and loss of reflexes. There was recovery with the exception of the left thigh muscles which became atrophied, and the nerves showed a reaction of degeneration.

Kilham et al.[92] (1949) point out that in 1948, in Massachusetts, there was an unusual incidence of mumps between June and November and at the same time there was an appreciable increase in poliomyelitis cases. They felt that many of the cases of non-paralytic poliomyelitis that were reported were probably cases of mumps meningoencephalitis. They found that 6 of 17 hospitalized patients, diagnosed clinically as nonparalytic poliomyelitis, were actually caused by mumps in which the salivary gland involvement was not evident.

Van Bogaert [93] (1909-10) reported an epidemic of poliomyelitis superimposed on or complicating a severe epidemic of measles. Moser[94] (1912) mentions meningitis, encephalitis and poliomyelitis as sequelae of measles. Osler and McCrae[58] (1923) point out that polyneuritis with widespread atrophy may occur as a complication of measles. Donlegny and Baixe[95] (1931) reported peracute polyneuritis of the bulbar type following measles. Panto[96] (1934) reported a case of flaccid paralysis ten days after the onset of measles in an infant of two years. Lafuente[97] (1943) pointed out that measles was considered to be the most frequent cause of paralysis in Mexican children.

Paralysis has been reported during the course of and following smallpox. Wilson and Ford[98] (1927) noted that clinical symptoms in general indicate an involvement of the anterior horn cells of the spinal cord. Some of the cases reported in the literature have presented the clinical appearance of acute ascending paralysis (Landry's paralysis) and some were cases of anterior poliomyelitis. In a case reported by Damaschino[99] (1860), a child two and one-half years old, had variola. During convalescence the lower limbs became weak. When examined six months later the affected

limbs were flaccid and had lost electrical contractility. At autopsy a focus of softening was found in the anterior part of the gray matter of the left side in the lumbar region of the spinal cord, and the nerve cells of the anterior horns were atrophied. The alteration in the cervical and thoracic regions were much less intense than in the lumbar region. In a case reported by Westphal[100] (1874), the gray matter of the cord was most affected and was infiltrated by fatty granular cells. Paralysis occurring in variola was reported in a man aged 20 years by Oettinger and Marinesco[101] (1895). Both gray and white matter of the lower thoracic region were affected but the gray more than the white. Perivascular infiltration of mononuclear and polymorphonuclear leukocytes were found in this portion of the spinal cord. Spiller[102] (1903) reported a case of anterior poliomyelitis during the course of smallpox in an adult and a case was reported also by Van Gehuchten[103] in the same year.

It was noted by Holt[11] and others, over fifty years ago, that poliomyelitis not infrequently followed anti-smallpox vaccination. In recent years there has been renewed interest in poliomyelitis following vaccinations and immunizations. Paul [104] reported a severe case of poliomyelitis following vaccination in 1928. Jeremburcz[105] (1930) reported two cases of poliomyelitis in connection with smallpox vaccination and in the same year Heidema[106] also made a similar report. In 1935, Banerjea[107] reported a case of poliomyelitis following vaccination of an infant for smallpox and, in 1940, Cervini and Tiscorma[108] reported the development of flaccid paralysis of the lower limbs ten days after smallpox vaccination in an 18-month-old child.

Attention was focused on the simultaneous occurrence of cases of postvaccinal neurological manifestations and poliomyelitis in England by Turnbull[109] as early as 1912, when he was investigating an epidemic of poliomyelitis. In 1923,[110] the issue of vaccine tubes began to rise that year about the middle of June, attaining its height in the last fortnight of July. Postvaccinal neurological manifestations appeared in the middle of June, reaching a maximum in the first half of August. The period of 1923, during which the majority of the postvaccinal cases occurred, was immediately antecedent to a rise of poliomyelitis and polioencephalitis. Following these observations in England, the association of vaccination with poliomyelitis and encephalomyelitis was noted in

the Netherlands, Czechoslovakia, Switzerland and other countries.

"Whooping cough, while less frequently than most other acute infectious diseases of childhood, is the forerunner of paralysis sometimes preceding its cerebral, spinal, and peripheral types."[37] Bassette[37] (1892) described a case of paralysis of the right leg in a 15-month-old child following whooping cough. Baginsky[111] (1911) speaks about the forms of paralysis in whooping cough, other than those caused by cerebral hemorrhages, that result from lesions in the brain or spinal cord. He reports a typical, ascending Landry's paralysis with rapid fatal termination in a boy of seven years of age occurring in connection with whooping cough. He states that there are individual cases of spastic spinal paralysis, of encephalitis with paraplegic symptoms, of multiple sclerosis with beginning bulbar symptoms and later a spastic paralytic condition, of polyneuritis with paraesthesia, anaesthesia and paralysis. Borrell[112] (1932) reported the development of a case of acute poliomyelitis in an infant with whooping cough.

It has been reported in recent years that whooping cough inoculations can be followed in some cases by the development of encephalomyelitis.[113-119] Coinciding with these observations, it has been noted in the past few years, and with increasing frequency since the original reports by Australian and British observers,[120-126] that poliomyelitis can also follow immunization against either or both whooping cough and diphtheria, as well as after immunization with the combined antigens of diphtheria, whooping cough and tetanus. The neurological reactions to these immunizing agents have been attributed to a toxic substance or a poison-like antigen formed by the immunizing agent which so affects the nervous system that paralysis results.

The administration of rabies vaccine is occasionally followed by paralysis of the dorsolumbar or Landry's paralysis type. These paralytic accidents have been attributed to the brain tissue substance in the offending material.

Two separate epizootics in animals of definitely established bacterial etiology which resulted in poliomyelitis, reported by Gard[127] (1944), appear to be of great significance. The first of these appeared in July 1941 when a number of young guinea pigs were bought and housed in the same stable room with a stock of mice. After two weeks some of the guinea pigs became ill

and within two months all of them died. It was found that the lymph nodes, especially the mesenteric glands, were enlarged and hyperemic. In cultures from mesenteric glands, salmonella enteritidis was constantly recovered, usually in pure culture. When this discovery was made the infection had already spread to the mice. During the height of the epizootic, the last week of August and the first week of September, four cases of poliomyelitis occurred in the mice. All four mice showed, besides the nervous system lesions, fatty degeneration of the liver and their mesenteric glands resembled those of the guinea pigs that were affected by the salmonella bacillus.

The second outbreak occurred in June 1943. As early as the middle of May an epizootic among stock mice had become evident affecting chiefly the young. At the height of the epizootic practically all young mice were attacked and most of them died. The initial symptoms consisted of a slimy or watery profuse diarrhea. The intestinal contents on culture yielded B. proteus vulgarus in some cases and by direct microscopy a large number of amebae, infusorians, and flagellates were observed. Adult mice, usually only females in the first week after delivery, when attacked were usually found dead without having displayed any obvious symptoms. Smears from the liver revealed the B. piliformis, and Gard considered this organism to be the cause of the epizootic. During the outbreak five cases of poliomyelitis developed among the mice.

COMMON DENOMINATORS OF CAUSE AND EFFECT

Sporadic cases of poliomyelitis may occur during any season of the year but epidemics occur particularly during hot weather when absolute humidity is high. Armstrong[128] (1951) found that poliomyelitis is most prevalent while the relative humidity level is above 28 per cent and the temperature above 90° F. Corresponding with these observations is the lesser known fact that poisons and toxins may produce clinical neurological manifestations more frequently in hot weather than during other seasons of the year. Lead,[129-133] for example, which has been described as one cause of poliomyelitis is an outstanding example.

Suzuki and Kaneko[134] (1924), as well as Fukushima and Matsumato[135] (1928), noted a seasonal incidence of lead poisoning. Blackman[136] (1937) demonstrated the onset of lead encephalitis

in 19 of 22 cases between the months of June and October. Rappaport and Rubin[137] (1941) observed the manifestations of lead encephalopathy between the months of May and September. Giannattasio et al.[138] (1951) reported fourteen cases of lead poisoning in children, 12 of which occurred between June 1951 and September 1951.

Blackman[136] suggested that this seasonal incidence of lead poisoning may be due to precipitation of the central nervous system lesions by factors which cause vasodilatation, such as fever and the heat of the summer and early fall months. Rappaport and Rubin[137] suggested that sensitization by sunlight of increased amounts of porphyrin in plumbism may contribute to the seasonal incidence.

This reference to porphyrin in plumbism is important inasmuch as it has been demonstrated that coproporphyrin III is present in the urine of experimental and clinical lead poisoning, as well as in poisonings by other substances. Analogous urinary findings of coproporphyrin III have been observed in cases of poliomyelitis by Watson et al.[139, 140] (1947). Salter[141] (1952) points out in his Textbook of Pharmacology that the porphyrins are of interest because they bear witness to a derangement in metabolism which usually reflects the presence of some other poison.

That the atmospheric and climatic conditions of the summer and fall are responsible for the development of neurological complications and sequelae in infectious diseases, and following vaccination and other immunological procedures, is apparent from the facts that have already been considered in this paper. The question naturally arises, "Does a toxin produced by an infectious disease organism as well as an antigen contained in immunizing agents become neurotrophic when atmospheric and climatic conditions are favorable." The observation by Gard,[127] that the poliomyelitis which resulted from the salmonella enterides infections in mice between July and September 1941, and the B. piliformis infections that resulted in mouse poliomyelitis in the summer of 1943, as well as the recent observations that vaccinations and other immunizing procedures during the summer are followed sometimes by poliomyelitis, strongly suggest this possibility.

Other facts must be considered in explaining some cases of poliomyelitis. For example, the poliomyelitis epidemic season,

May to September or October, corresponds with the growth and harvest of perishable fruits and vegetables. During this period drought conditions favor the development of intrinsic poisons in plants and the increased use of poisonous insecticides which for some individuals may have a neurotrophic effect.

It is a well-known fact that fatigue is an important factor in precipitating an attack of poliomyelitis. A similar physiological alteration of the body will bring about the neurological manifestations of poisoning by lead and other poisons. A similar situation seems to exist in relation to trauma, chilling, operations, pregnancy, etc. in poliomyelitis and various forms of poisoning.

There is evidence that a disturbance in the biochemistry of the nervous tissues occurs both in poliomyelitis and poisoning. In other words, some enzyme system of the central nervous system concerned with the synthesis of some essential structure of the cell appears to be affected in each case. In the complex physiological and biochemical cycles of the nerve cell, there are several enzymatic systems intimately interrelated, a disturbance of any one of which might disrupt the function of the cell as an organized unit. The end result is the same, i.e. motor neurone injury or destruction. That the mode of action of the various etiological agents capable of producing poliomyelitis is at least similar if not identical, is suggested by the similarity of the resulting lesion.

SUMMARY

1. In the absence of a specific diagnostic test for poliomyelitis, the diagnosis of the vast majority of cases has been dependent merely on personal judgement.

2. There is evidence that poliomyelitis has many causes rather than a single cause.

3. Common denominators of cause and effect in all cases appear to depend on seasonal and climatic conditions, fatigue, trauma, etc., and disturbances of the physiology and chemistry of the nerve cell.

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PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

RHEUMATISM IN CHILDREN*

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However obscure may be the pathology of rheumatism, one factor at least has been definitely ascertained, namely, that it is a disease that differs widely in its clinical manifestations and phenomena as we pass from childhood to adolescence, and again into adult life. We are perhaps too apt to suppose that rheumatism is a comparatively simple disease, whereas closer observation tends to prove that it is a great complex, somewhat akin to gout in the variety of its clinical manifestations. Indeed, the symptoms of rheumatism, as they are generally accepted, may be so slight or masked during the earlier years as to escape detection, or if of a degree sufficient to attract notice they are often so vague or erratic as to be attributed to other pathologic conditions; on the other hand, the symptoms of other diseases may be so suggestive of rheumatic evidences as to lead one to an erroneous diagnosis. We all are too prone to rely upon the arthritic symptoms to reach our diagnosis, and to ignore other evidences quite as characteristic. The symptoms, as they appear in childhood, are so different in their order and degree that one may most naturally be misled unless he is familiar with their differences and unbiased by his experience with the disease as he has seen it in adult life.

The theory formerly held as to its cause has undergone marked change; the cause of then is an effect of today. Excess of lactic acid in the blood had been held for many years the causative factor of the disease. Foster, of Birmingham, in 1871, stated that in two patients to whom he had given lactic acid in 15 to 25 m. doses there had developed painful swelling of the joints. (This experi-

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ment has never very satisfactorily been verified by other investigators.) A socalled plausible theory of the day was that, under the influence of cold, lactic acid, which is always formed as a result of muscular action, fails to be destroyed by oxygenation, as it should be, and that when so accumulated it acts as an irritant to the joints. We now do not accept this as a causative agent; it may be that the blood is surcharged with lactic or other acid (but this is very difficult of proof), but even if so, it must be the result of a toxin of some infective agent circulating in the blood.

In the light of our present knowledge in other diseases the clinical and hygienic aspects of rheumatism present all the characteristics of an infectious illness. Investigation along this line began as early as 1887, by Pohoff; later by Triboult, in 1898, both observers noting a tiny micrococcus, usually occurring in chains or pairs. Westphal, Wassermann and Machoff, in 1899, in Berlin, found the same organism in a fatal case of chorea. More recently Paine and Poynton have described, under the title of "Micrococcus Rheumaticus," a diplococcus or a streptodiplococcus, which fulfils all the conditions as the specific cause.' They say: "So soon as the micrococcus rheumaticus can with certainty be distinguished from all other micrococci which tend to grow in chains, we shall have the definite and essential point to attack the vast array of clinical conditions grouped as rheumatic or rheumatoid." It has been proven that a particular microorganism is constantly associated with rheumatic lesions, it can be cultivated upon artificial media outside the body, and by inoculation gives rise to characteristic lesions of the disease, and can again be isolated from these lesions. Culturally, this organism resembles a streptococcus, but that it is specifically different is rendered probable by the test of Marmorek, who found that if a fluid medium in which streptococci of human origin have grown be filtered free from microorganisms and again be employed as a culture medium, bacteria in general can flourish in the fluid, while streptococci of human origin are entirely unable to multiply in it. Such a fluid, therefore, may be used as a test solution to determine whether a given organism obtained from man is identical with ordinary human streptococci or is different from it. Beaton and Walker applied this method to two specimens of the micrococcus rheumaticus on two occasions with positive results; in every case the micrococcus rheumaticus grew freely in a medium of filtered streptococcus bouillon, exhibiting considerable chain

formation; this being true, it follows that the micrococcus rheumaticus is specifically different from the ordinary pyogenetic streptococci of human origin, and the specificity of the micrococcus rheumaticus is established. It has been isolated in all of the 15 cases examined by Beaton and Walker, eight times in acute rheumatism, three times in chorea, and four times in endocarditis of rheumatic subjects; it was secured from the heart's blood, fluid from the knee joint, urine, venesection, and from the blood from the ear. Paine and Poynton isolated this diplococcus in 22 cases of rheumatic fever, and have demonstrated it in the principal lesions. They grew in pure culture and have produced by intravenous inoculation into rabbits identical lesions from which in turn they had isolated the bacterium. Seventeen rabbits, inoculated into the venous system, manifested the following results:—fever, wasting, monoarthritis, polyarthritis, paresis of the limbs, peri- and endocarditis, septicemia and death. The above pretty thoroughly establishes the bacterial specificity; the toxic specificity is still unsolved, but that some toxin circulates in the blood is evidenced by the concurrence of pyrexia, rapid anemia, erythema and purpura, polyarthritis, peri-, endo- and myocarditis.

As predisposing causes, cold and heredity occupy undoubtedly leading positions; it is a disease of families, and this fact alone is an aid in reaching a diagnosis. Age manifests the same irregularity in children as the other factors of the disease; among children girls are more subject to it than boys, but as the years advance this gradually changes, until in adult life men are more often the victims of rheumatism than women. It was formerly considered rare, or comparatively so, among the young; this still holds good so far as infants are concerned, but it is now recognized as much more common in childhood than formerly, due no doubt not to a change in the disease, but to a more careful examination of its vague manifestations. The arthritic implication is often so slight that it escapes notice or is attributed to other causes; redness and swelling of the joints are rare, and possibly only a tenderness or sensitiveness in the region is noticed; sometimes lameness or a disinclination to move about for a day or two is the only evidence; with this there may or may not be slight fever, never the degree of fever we are accustomed to find in older patients. Hyperpyrexia, or even high fever, is most exceptional, as are also the profuse acid sweats.

Tonsillitis or pharyngitis may be the first and only evidence of the rheumatic state; and in this particular Paine and Poynton isolated from a rheumatic sore throat the diplococcus which, upon intravenous inoculation into rabbits, produced arthritic symptoms and endocarditis. Torticollis and socalled growing pains are apt to be of rheumatic origin. Chorea, so long allied to rheumatism, may usually, upon closer inquiry, be traced to some antecedent history. The skin manifestations, purpura and erythema, are much more prevalent among children than adults.

Subcutaneous nodules, as commonly referred to by English writers, though evidently of rarer occurrence among us, are considered an especial feature of the disease among children. As described by Cheadle, "they are nodules which lie under the skin in connection with the fascia and tendons, that is in relation with the fibrous tissue; and similar nodular proliferations have been found in the periosteum, and even in the pericardium. They vary in size from that of a hemp seed to that of an almond, or even larger; when small they may not become visible until the skin is drawn tightly over them, although easily detected by the touch. There may be but one of these nodules, though usually three or four are found; indeed, sometimes as many as twenty or thirty. Their duration varies from a few days to several months. They indicate concurrent usually progressive cardiac disease, and that a similar process of inflammatory change and proliferation is going on in the fibrous tissue of the cardiac valves and pericardium. When many and large they indicate serious danger, an endo- or pericarditis, which is uncontrollable and advances almost certainly to a fatal ending. The connection of these nodules with rheumatism and rheumatoid arthritis is apparently absolute; so far as is known they own no other origin or relation." This has been quoted somewhat at length as so slight reference is made to them by American observers, while such stress and importance are placed upon them by foreign writers.

The most important as well as the most grave manifestation of the disease is the cardiac. I do not say complication but manifestation, as it is as much a symptom as nearly any other phase of rheumatism; the earlier in life rheumatism shows itself the more probable is the cardiac involvement, and the more severe the other symptoms the more liable is the heart to be damaged during its course; this is estimated to occur twice as frequently in children

as in adults. It is a disease that attacks every structure of the heart; the endocardium, pericardium and myocardium are involved about in the order named. There is great diversity of opinion as to their involvement, but the great majority of observers estimate that sooner or later—due to the age, severity or frequency of attacks—one-half to one-third of all its victims manifest cardiac lesions. "It has been stated that endocarditis is liable to come on so insidiously, without its existence being known or suspected, until some other rheumatic manifestation leads to an examination of the heart and to the discovery of valvular mischief already established." Even when discovered during the course of the disease, the symptoms are vague, slight and slowly developed. There may be first only a quickening of the pulse with an excited, uneven, irregular action of the heart, before any changes in the cardiac sounds are noticeable. Any valve may be attacked, but by far the most common is the mitral, next the aortic. Probably the first physical sign to appear will be a soft blowing, systolic murmur, heard at the apex, with possibly a slight accentuation of the second pulmonary, which points to a beginning leakage of the mitral. There is some discussion among observers whether these early cardiac symptoms are due to an endocardial or a myocardial mischief; if to the latter, that they are due to an acute dilatation caused by the action of a toxin upon the muscular structure, but practically this is of minor importance, as we fully realize that under either condition serious changes do finally result.

No physician who has had hospital or private practice can fail to be impressed with the number and seriousness of the cases of organic heart disease that come under his notice; the enfeebling and shortening of valuable lives which occur from this cause, particularly when the injury to the heart occurs, as it commonly does, early in life, must appeal to him both as a humanitarian as well as a citizen of the community. If this paper has any object in view it is to urge closer observation for the detection of the disease early in its course, and to discuss what measures, if any, may be suggested to modify or avoid the grave consequences of the disease as seen in chronic valvulitis.

The pathological changes in the valves of the heart, as well as the later symptoms, have intentionally been omitted from this paper, partly on account of time, but more particularly because both have been so fully dilated upon in textbooks, besides one's

personal experience renders them familiar to all practitioners. In regard to the early diagnosis of rheumatism in children in doubtful cases the following points of investigation may be of assistance:—

1. *Family History.* The influence of heredity is undoubted. Cheadle reports that 70 per cent of his private cases reported rheumatism in near blood relations. The double inheritance (that is, on both father's and mother's side) increase to a remarkable degree the tendency to the disease.

2. *Previous History.* As regards joint stiffness without swelling, growing pains, nose bleed, frequent attacks of tonsillitis or erythema.

3. *Present Condition.* The appearance of the child, whether thin and anemic with lack of appetite and malaise, a disinclination to take part in the games of their playmates; bronchial or gastric catarrh, purpuric-like spots over legs, that are not due to bruises, are all suggestive.

4. *Temperature.* Attacks of slight fever without apparent cause. Brunton in an article on "Endocarditis and the use of the Thermometer in its Diagnosis" goes so far as to say: "If you find a murmur at the heart, or even where you find *no* murmur, if you find a temperature which runs a course like that of quotidian ague in a case where you can trace no malaria, and where you find no indication of suppuration, it is very likely indeed to be a case of endocarditis." Undoubtedly slight febrile attacks occurring in children do often furnish possibly the only evidence of rheumatic involvement; and the effort on our part to discover the cause of these slight variations in temperature will often lead us to the proper diagnosis.

5. *Examination of the Heart.* Especially as to its rate and rhythm, early evidences being cardiac irritability marked by excited action, with rhythmic changes, especially of remission and intermission; later physical signs appear—a soft murmur at the apex with reduplication of the second sound also at the apex, due probably to a retarded opening of the mitral; there may also be an increase in the cardiac area due either to a dilatation or even so early to a compensatory hypertrophy, as the compensation in children is much more prompt and efficient, due probably to a more sensitive muscular structure during its period of growth.

If from such an examination we are led to suspect rheumatism, what can we do to attempt to avoid the serious heart lesions?

Of course, if any results are to be hoped for, the disease must be recognized early before serious destruction has taken place.

Naturally, the first thing to suggest itself is prophylaxis; that is, to protect in every way children in whom we know there exists a vicious tendency to the disease, from its exciting causes, such as cold, dampness or any undue exposure, lack of proper clothing which may be liable to favor its development. Those children in whom we have already recognized evidences of the disease without as yet cardiac symptoms we should guard against recurrence, as every fresh attack renders more probable the cardiac involvement.

Treatment. To avoid or cure slight heart manifestations undoubtedly certain measures may be instituted that will in many instances be provocative of encouragement. The first is—

Rest. In this particular Sir Wm. Jenner says: "Children do not grow out of heart disease, they grow into it." By rest we mean absolute quiet, no muscle work is permitted except such as is required for life; in this way we try to restrain the force and velocity of the blood current and lessen, if possible, the work of the heart, and diminish the pressure of the blood on the beginning diseased valves, as well as to lengthen the brief rest periods of the heart between its systoles. All stimulating food is withheld and only a slight, simple, easily digested diet is given; the patient is kept in strict recumbency, no getting out of bed or even raising the head. At the same time the patient should be shielded from any mental agitation or excitement. Holt says: "That the rest should be measured by months rather than weeks, and that the recumbent posture should be maintained until sitting upright is not attended by acceleration of the pulse rate or changes in its rhythm." It is pretty generally acknowledged that a beginning endocarditis, even when physical signs are evident, can often be cured if the heart work is kept at the minimum. Undoubtedly such stringent measures are often difficult to institute, but if the serious consequences are made plain to the parents and the possibilities of their avoidance is explained, much cooperation may be secured.

R. Caton, of Liverpool, who has probably given greater attention to the avoidance and cure of early heart lesions, adds two other measures to be instituted in the course of the rest treatment; the first is

Counterirritation over the upper part of both sides of the chest between the clavicle and the nipple, by the application of small blisters about the size of a quarter. His theory is as follows: "If the stimulation of the surface skin will so potently assist recovery in a rheumatic joint, is it not possible that some beneficent change might also occur in the rheumatic heart if continued stimulation of its related skin areas were practised? The upper, middle and lower cardiac nerves on each side are associated with the three cervical ganglia of the sympathetic, and through them, probably, with the upper eight dorsal intercostal nerves. Through the upper and middle cardiac nerves (which communicate with the pneumogastric) the heart appears to be much more closely in relation with the first four dorsal intercostal than the remainder. This cutaneous surface and its nerves being so intimately related to the heart, it appears quite probable that through the sympathetic that the rheumatic heart might follow stimulation similar to those which occur in a blistered rheumatic joint." Though his explanation seems very involved, his results have led him to place great reliance upon this procedure. His other suggestion as an adjuvant to the above two is the employment of absorbent drugs, sodium or potassium iodid and mercury in the form of calomel. Naturally, he has been criticised for not experimenting with only one of his three measures at a time, to discover if one only of these be the really efficient agent, his answer to this being that his success with the combination has yielded such good results that he does not feel disposed to dispense with any one.

Caton gives a detailed report of 86 cases so treated, divided into two classes. First, those in which the endocardial mischief came on under his observation—there were 31 such cases, of which 28 made a good and apparently permanent recovery. Second, those in whom the valvular trouble was manifest before they came under his observation (of course, of recent origin). Of these there were 55, of whom 36 left the hospital with apparently sound hearts.

This is a most remarkable and gratifying report from an observer recognized as capable and painstaking, and certainly such results warrant greater effort on our part to attempt to ward off a condition that cripples the usefulness of such a large number of individuals.

DEPARTMENT OF ABSTRACTS

Applebaum, E.; Greenberg, M. and Nelson, J.: Neurological Complications following Antirabies Vaccination. (Journal American Medical Association, 151:188, Jan. 17, 1953).

Experience in 46 cases of encephalomyelitis following vaccination with rabies virus in New York City from 1928 to 1951 is summarized. There were no deaths. The clinical manifestations are described according to the three general types encountered: encephalitic, dorsolumbar myelitic and neuritic. The spinal fluid was usually clear, with an increase in cells, predominantly lymphocytes. The protein content was normal, and cultures were sterile. There is no specific treatment. The use of cortisone and corticotropin requires further investigation. The epidemiological features are discussed. The incidence of encephalomyelitis was one accident to 2,025 persons treated in New York City Department of Health Clinics, but it was about five times higher in those who received 14 injections than in those who received 7 or fewer injections. The risk of rabies from a bite is shown to be greater than that of encephalomyelitis from vaccination. Criteria for use of vaccines are given, and avianized vaccine and antirabies serum are discussed. Authors' Summary.

Steigman, A. J. and Scott, C. H.: Trypsin in Poliomyelitis Patients with Tracheotomy. (Journal American Medical Association, 150:1403, Dec. 6. 1952).

Development of viscid tracheobronchial secretions is a problem in tracheotomized poliomyelitis patients. These secretions can be treated by adequate systemic hydration, humidification of air, antibiotics, both locally and systemically, tracheal instillation of saline, etc. However, in spite of all measures, tenacious viscid secretions often result in impairment of ventilation. The authors have used crystalline enzyme trypsin (tryptar) with favorable results. The solution used contains 250,000 U. of trypsin, 1,000,000 U. of aqueous penicillin, 60 mg. of phenylephrine hydrochloride, and 50 ml. of Sorenson's phosphate buffer solution (pH of 7.1). About 3 ml. of the solution is instilled into the tracheotomy tube. After waiting 3 to 5 minutes, swift aspiration of the tracheobronchial tree is performed with a soft rubber catheter. By turning the

patient's head sharply to the right it is generally possible to enter the left main stem bronchus and vice versa. No signs of local or systemic irritation have been noted. The authors were frequently gratified to find that the stringy tenacious exudate assumes a semi-liquid character following treatment.

MICHAEL A. BRESCIA, M.D.

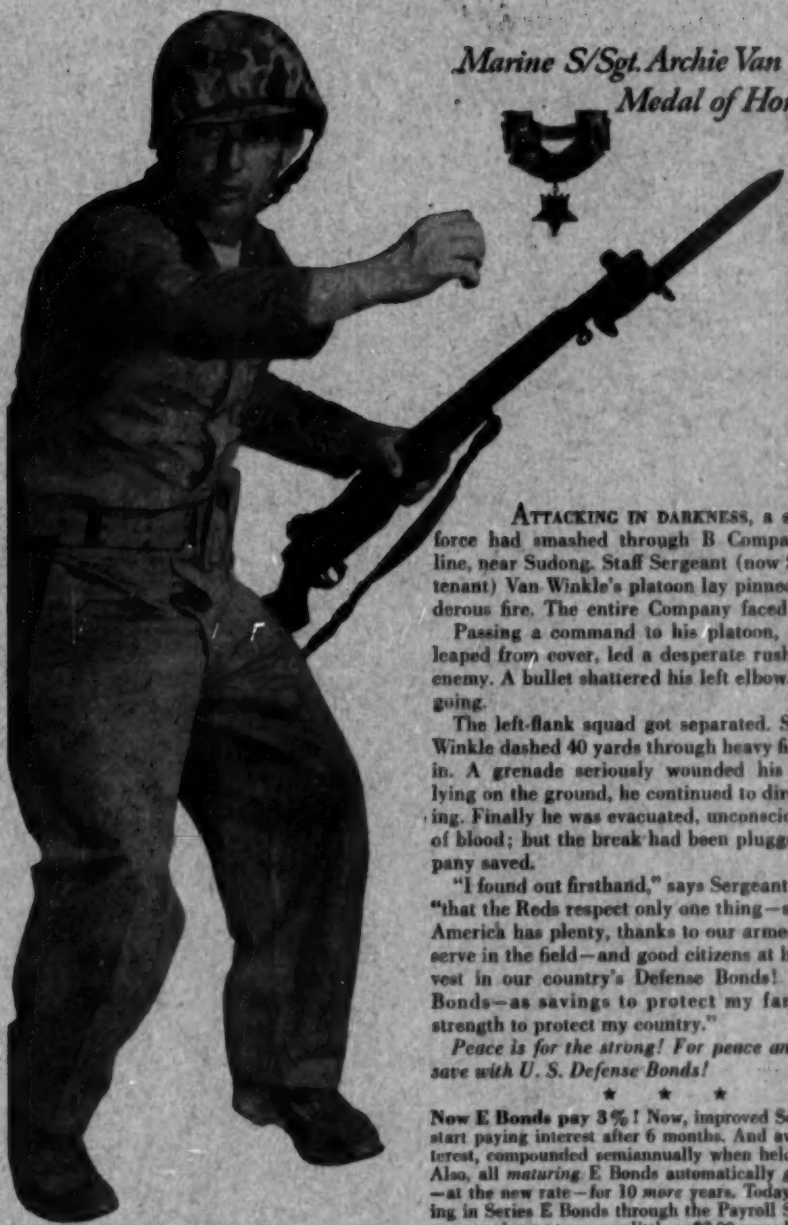
TAUSSIG, H. B. AND BAUERSFELD, S. R.: FOLLOW-UP STUDIES ON THE FIRST 1,000 PATIENTS OPERATED ON FOR PULMONARY STENOSIS OR ATRESIA—RESULTS UP TO MARCH 1952. (Annals of Internal Medicine, 38: 1, Jan. 1953).

The results of the first 1,000 operations have been analyzed on the basis of those with tetralogy of Fallot and those with atypical malformations. The long-time results have been analyzed according to whether the patient obtained a good or a fair result or was unimproved by operation. Those who obtained a good result have done far better than those who obtained a fair result. In the entire series there have been 53 late deaths, 43 in the group of patients with tetralogy of Fallot, and 10 among those with atypical malformations. The mortality rate has been significantly lower among those who obtained a good result than in the other two groups. One hundred-fourteen patients have failed to maintain improvement; 28 of these have had a second operation, and the others are still pending. During the 7-year-period since the first operation, there have been but 22 cases of subacute bacterial endocarditis, with 4 deaths. AUTHORS' SUMMARY.

GALLOWAY, T. C.: RELATIONSHIP OF TONSILLECTOMY TO POLIOMYELITIS. (Journal American Medical Association, 151:1180, April 4, 1953).

From my study of the evidence it seems that the following conclusions are tenable: Tonsillectomy does significantly increase the incidence of bulbar poliomyelitis when done during epidemics. The over-all incidence is probably increased but perhaps only by the increase of bulbar poliomyelitis. Elective tonsillectomies should be restricted in epidemic periods. Investigation should be made of a similar relationship of dental and other oral and general operations to poliomyelitis and the need of restricting them in epidemic.

AUTHOR'S SUMMARY.



Marine S/Sgt. Archie Van Winkle
Medal of Honor

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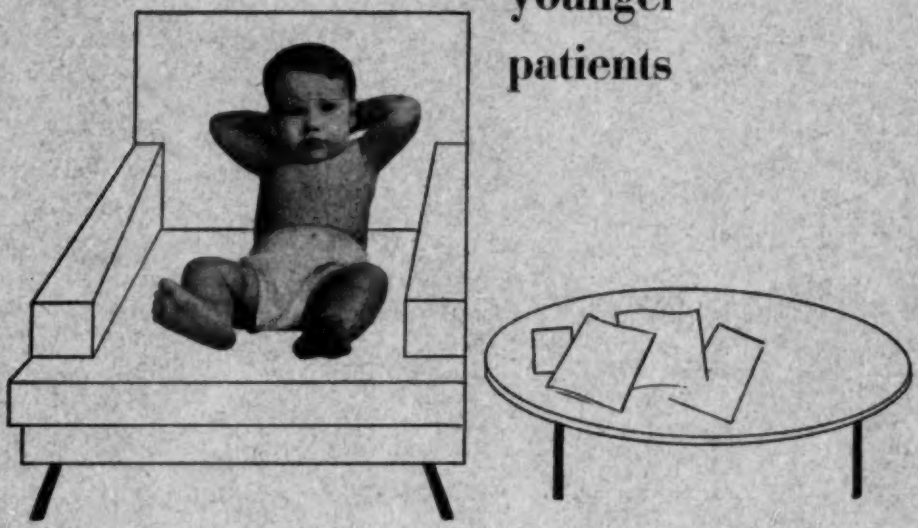

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